

GENE EXPRESSION STUDIES IN ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES

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National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

(<http://www.niams.nih.gov/>)

LETTER OF INTENT RECEIPT DATE: February 17, 2003

APPLICATION RECEIPT DATE: March 17, 2003

THIS RFA CONTAINS THE FOLLOWING INFORMATION

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PURPOSE OF THIS RFA

This solicitation is intended to facilitate the use of comprehensive gene expression analysis technology in basic and clinical research relevant to arthritis and musculoskeletal and skin diseases. The NIAMS invites two types of applications. First, Principal Investigators who are

currently supported by research project grants from the NIAMS are invited to submit competing supplement applications, proposing the expansion of the scope of the projects to include use of comprehensive gene expression analysis technology. Second, scientists with established expertise in arthritis or musculoskeletal or skin diseases are invited to propose new projects in which comprehensive gene expression analysis technology is a major and essential component, and in which new insights are likely to be obtained that would not arise from the use of conventional analytical techniques.

RESEARCH OBJECTIVES

Background and Rationale

In recent years, a variety of techniques have been developed that allow for the assessment of messenger RNA levels for very large numbers of genes in a single procedure. The most commonly used tools are high-density arrays of hybridization probes, which have been produced using either synthetic oligonucleotides or cloned DNA fragments. High-throughput sequencing of concatenated DNA fragments has also shown promise. The adoption of these techniques has presented a number of challenges, both technical and conceptual. Technical problems include the specialized and costly nature of the required equipment, the substantial degree of skill and experience required to make use of the techniques, the limited availability of standardized probe collections, and the bioinformatic problems of analyzing very large datasets. Conceptually, it has been difficult to frame rigorous hypotheses and models that integrate the enormous amount of detail obtained in these experiments with broader questions in biology and medicine. This solicitation is intended to focus available resources on those applications of gene expression analysis that hold the most immediate promise of contributing to rigorous investigations in areas within the NIAMS mission.

Objectives and Scope

Proposed research must support the NIAMS mission as detailed in the NIAMS World Wide Web home page, which can be found at <http://www.niams.nih.gov/rtac/funding/faq.htm>. In brief, the NIAMS supports research in: rheumatic diseases; cartilage biology and diseases; bone biology and diseases (e.g., osteoporosis, Paget's disease); skin biology and skin diseases; autoimmune diseases (e.g., lupus, rheumatoid arthritis); connective tissue diseases; musculoskeletal diseases (e.g., osteoarthritis); musculoskeletal imaging; injuries and disorders of the musculoskeletal system; muscle biology and diseases (e.g., muscular dystrophy); exercise physiology and

musculoskeletal fitness; sports injuries; occupational diseases and injuries; and orthopaedic and bioengineering topics.

Applications will be accepted across the spectrum of biological models and diseases within the NIAMS mission. The primary objective of this initiative is to focus resources on specific biological and medical problems for which the immediate application of comprehensive gene expression analysis technology has the potential to yield significant new insights. For example, characterizing gene knockout or transgenic mouse strains, in which genetic variation from controls is limited and known, should produce manageable datasets, and may indicate the downstream targets of inactivated or introduced genes. In more complex situations, computational approaches such as hierarchical clustering can group genes into subsets showing coordinated expression patterns, presumably reflecting related functions. However, such an approach must be firmly grounded in established biology.

A second objective is to direct support to groups that are in the best position to make use of comprehensive gene expression analysis technology at this time. These are likely to be groups with access to necessary equipment, and with substantial previous experience in the use of the technology. Alternatively, investigators may establish collaborations with other scientists having the requisite expertise, or make use of commercial products and services that standardize aspects of the technology.

Examples of situations in which a response to this RFA may be appropriate include, but are not limited to, the following:

- o On-going NIAMS-funded projects in which comprehensive gene expression analysis was not originally included in the research design, but in which such analysis can be justified in pursuit of the original aims.
- o On-going NIAMS-funded projects in which results to date justify expansion of the scope to include new but related aims requiring comprehensive gene expression analysis.
- o On-going NIAMS-funded projects in which comprehensive gene expression analysis was included in the original design, but in which the originally budgeted funds have proven inadequate to support rigorous application of the technology.
- o New projects in which existing comprehensive gene expression data, (e.g., from publicly accessible data resources) will be analyzed to achieve aims relevant to the NIAMS mission.

- o New projects requiring comprehensive gene expression analysis, and making use of existing patient cohorts or specimen archives, whether the original development of the resource was NIAMS-supported or not.

- o New projects that would have been impractical to undertake with older analytical methods, but which may be tractable with the application of comprehensive gene expression analysis techniques.

MECHANISM OF SUPPORT

This RFA will use NIH competing supplement and investigator-initiated research project grant (R01) award mechanisms. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. Future unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures. The anticipated award date is September 2003.

Competing supplement applications are subject to the requirements stated in the Form 398 instructions (see [ftp://ftp.grants.nih.gov/forms/phs398.pdf](http://ftp.grants.nih.gov/forms/phs398.pdf).) Briefly, a competing supplement application may be submitted to request support for a significant expansion of a project's scope or research protocol. The principal investigator must be the same as the principal investigator of the parent application. Supplemental applications must include both a Progress Report for the current grant and an Introduction, providing an overall description of the nature of the supplement and how it will influence the specific aims, research design, and methods of the current grant. Only R01, P01, R37, P30, P50, P60, and U01 awards are eligible for supplements under this initiative. In order to be considered for a supplement, the current grant must have at least two years of funding remaining at the time of the supplement award. A supplement request may not extend beyond the parent grant. Applicants must identify supplemental applications by checking the "Supplement" box on the Checklist page and entering the number of the currently funded grant for which the supplement is being requested.

This RFA uses just-in-time concepts. It also uses the modular budgeting format. (see <http://grants.nih.gov/grants/funding/modular/modular.htm>). Specifically, if you are submitting an application with direct costs in each year of \$250,000 or less, use the modular format.

FUNDS AVAILABLE

The NIAMS intends to commit approximately \$2 million in FY 2003 to fund ten to fifteen supplements and/or new awards in response to this RFA. Supplement applications may request up to \$100,000 per year in direct costs. A supplement may not extend beyond the parent project award period. Research project (R01) grants may not exceed \$250,000 per year in direct costs. The total project period for an R01 application submitted in response to this RFA may not exceed four years. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of the NIAMS provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

- o For-profit or non-profit organizations
- o Public or private institutions, such as universities, colleges, hospitals, and laboratories
- o Units of State and local governments
- o Eligible agencies of the Federal government
- o Domestic or foreign

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Individuals with the skills, knowledge, and resources necessary to carry out the proposed research are invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are particularly encouraged to apply for support from NIAMS programs.

SPECIAL REQUIREMENTS

Data Sharing Plan

Because comprehensive gene expression analysis methods can record expression levels for thousands of genes, data may be useful for purposes beyond those prompting their original collection. Thus, applicants responding to this RFA must describe plans for making data available to other investigators. For example, they may identify existing publicly accessible data repositories, such as the NCBI Gene Expression Omnibus (<http://www.ncbi.nlm.nih.gov/geo/>) to

which data will be submitted. Data sharing plans must include a timetable specifying when data will be shared, relative to collection, analysis, and publication. Peer reviewers will be asked to comment on the adequacy of the plan. The requirement for data sharing will be incorporated as a condition of any award made under this RFA.

Annual meetings

The technology of comprehensive gene expression analysis presents new challenges and is still changing rapidly. It is important for investigators applying this technology to exchange information regularly. The NIAMS plans to organize annual meetings of investigators supported under this initiative, to facilitate this exchange of information. In preparing budget requests, applicants should anticipate expenses for annual travel to Bethesda, Maryland for this purpose.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

o Direct your questions about scientific/research issues to:

William J. Sharrock, Ph.D.
Musculoskeletal Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5055
FAX: (301) 480-4543
Email: ws19h@nih.gov

o Direct your questions about peer review issues to:

Richard Bartlett, Ph.D.
Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza

6701 Democracy Blvd, Suite 800

Bethesda, MD 20892-4872

Telephone: 301-594-4956

Fax: 301-402-2406

Email: bartletr@mail.nih.gov

o Direct your questions about financial or grants management matters to:

Michael G. Morse

Deputy Chief, Grants Management Branch

National Institute of Arthritis and Musculoskeletal and Skin Diseases

One Democracy Plaza

6701 Democracy Blvd. Suite 800

Bethesda, MD 20892-4872

Telephone: (301) 594-3535

FAX: (301) 480-5450

Email: nelsonm@mail.nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

- o Descriptive title of the proposed research
- o Name, address, and telephone number of the Principal Investigator
- o Names of other key personnel
- o Participating institutions
- o Number and title of this RFA

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

William J. Sharrock, Ph.D.

Musculoskeletal Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5055
FAX: (301) 480-4543
Email: ws19h@nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS: Applications requesting up to \$250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in \$25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at <http://grants.nih.gov/grants/funding/phs398/phs398.html> includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: <http://grants.nih.gov/grants/funding/phs398/label-bk.pdf>.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and three signed, photocopies, in one package to:

Center for Scientific Review

National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application must be sent to:

Richard Bartlett, Ph.D.
Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd, Suite 800
Bethesda, MD 20892-4872
Telephone: 301-594-4956
Fax: 301-402-2406
Email: bartletr@mail.nih.gov

APPLICATION PROCESSING: Applications must be received by the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an Introduction addressing the previous critique.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NIAMS. Incomplete applications will be returned to the applicant without further consideration. And, if the application is not responsive to the RFA, CSR staff may contact the applicant to determine whether to return the application to the applicant or submit it for review in competition with unsolicited applications at the next appropriate NIH review cycle.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIAMS in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

- o Receive a written critique
- o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score
- o Receive a second level review by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council.

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of your application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

- o Significance
- o Approach
- o Innovation
- o Investigator
- o Environment

The scientific review group will address and consider each of these criteria in assigning your application's overall score, weighting them as appropriate for each application. Your application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, you may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) SIGNIFICANCE: Does your study address an important problem? If the aims of your application are achieved, how do they advance scientific knowledge? What will be the effect of these studies on the concepts or methods that drive this field?

(2) APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Do you acknowledge potential problem areas and consider alternative tactics?

(3) INNOVATION: Does your project employ novel concepts, approaches or methods? Are the aims original and innovative? Does your project challenge existing paradigms or develop new methodologies or technologies?

(4) INVESTIGATOR: Are you appropriately trained and well suited to carry out this work? Is the work proposed appropriate to your experience level as the principal investigator and to that of other researchers (if any)?

(5) ENVIRONMENT: Does the scientific environment in which your work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

o PROTECTIONS: The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

o INCLUSION: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria included in the section on Federal Citations, below)

o DATA SHARING: The adequacy of the proposed plan to share data.

o BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: February 17, 2003

Application Receipt Date: March 17, 2003

Peer Review Date: June/July 2003

Council Review: September 2003

Earliest Anticipated Start Date: September 2003

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

- o Scientific merit (as determined by peer review)
- o Availability of funds
- o Programmatic priorities.

REQUIRED FEDERAL CITATIONS

MONITORING PLAN AND DATA SAFETY AND MONITORING BOARD: Research components involving Phase I and II clinical trials must include provisions for assessment of patient eligibility and status, rigorous data management, quality assurance, and auditing procedures. In addition, it is NIH policy that all clinical trials require data and safety monitoring, with the method and degree of monitoring being commensurate with the risks (NIH Policy for Data Safety and Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>).

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the AMENDMENT "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals

and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS: The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at <http://grants.nih.gov/grants/funding/children/children.htm>.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at http://grants.nih.gov/grants/stem_cells.htm and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>.

Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see <http://escr.nih.gov>). It is the responsibility of the applicant to provide the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this RFA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas.

Potential applicants may obtain a copy of "Healthy People 2010" at

<http://www.health.gov/healthypeople>.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance No. 93.846, and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies described at <http://grants.nih.gov/grants/policy/policy.htm> and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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